Alkaloid Studies. 9.† Preparation of 18-Acylyohimban-17-ones and Their Conversion to New Heterocyclic Yohimbans

J. Donald Albright* and Leon Goldman

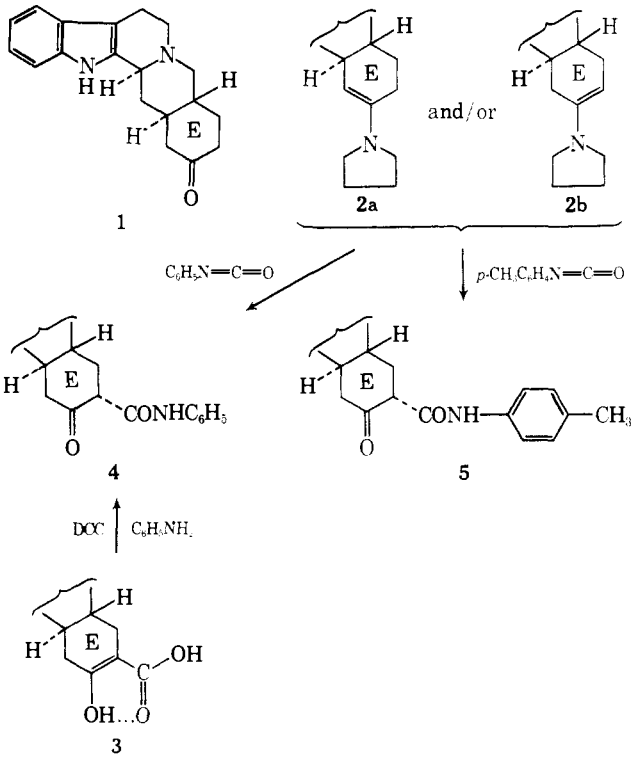
Organic Chemical Research Section, Lederle Laboratories, American Cyanamid Company, Pearl River, New York 10965. *August 9, 1973*

Heterocyclic derivatives of yohimban with an isoxazole, pyrazole, or pyrimidine ring attached to the E ring have been prepared by reaction of 18-acylyohimban-17-ones with hydroxylamine, hydrazine, guanidine, 2-methyl-2-thiopseudourea, and benzamidine. A number of the heterocyclic derivatives show CNS depressant activity.

Previous reports in this series have been concerned with the preparation of derivatives of yohimban-17-one and modification of these derivatives.[2] The introduction of substituents at the C-18 position of yohimban-17-one[2a] and the preparation of yohimbano[17,18-*c*]pyrazoles[2b,c] have been reported. The interesting tranquilizer activity found in these yohimbanopyrazoles prompted a search for additional C-18 substituted yohimban-17-ones which could be converted to new heterocyclic yohimbans.

Heterocyclic derivatives of yohimban-17-one (1) with an isoxazole, pyrazole, or pyrimidine ring attached to the E ring were prepared beginning with the synthesis of 18-acyl derivatives of yohimban-17-one.

Refluxing yohimban-17-one (1) and pyrrolidine in benzene with azeotropic removal of the water gave the desired enamine **2**. The reaction, however, could not be driven to completion as evidenced by the presence of carbonyl absorption in the product even after long reaction periods. This problem was surmounted to yield **2** in 90% yield by carrying out the reaction in a flask equipped with a Soxhlet extractor filled with aluminum oxide to remove the water which was azeotropically distilled. Whether the enamine isolated is a mixture of **2a** and **2b** or a single

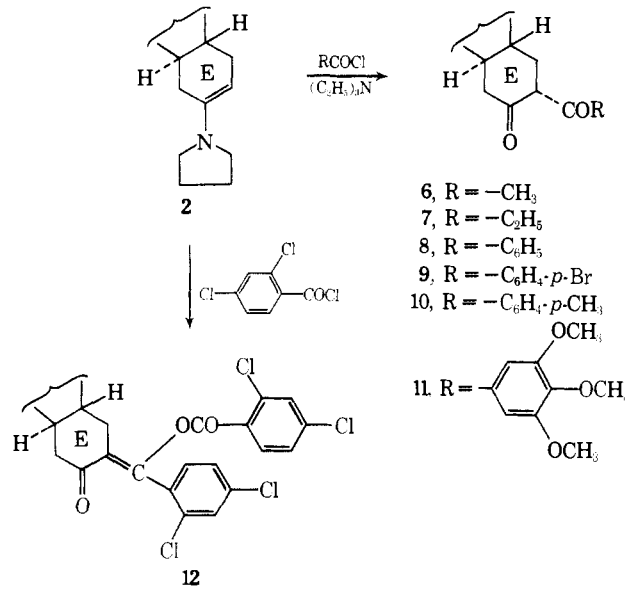


1 2a 2b 4 5 3

compound, we anticipated that reaction would occur at the C-18 position to give C-18 substituted products because of steric hindrance to substitution at C-16. Reaction of enamine **2** with phenyl isocyanate and with *p*-tolyl isocyanate gave the ketoamides **4** and **5**, respectively.‡,§ That substitution had occurred at C-18 was established in the following manner. Reaction of 17-oxoyohimban-18α-carboxylic acid[2a] (**3**) with *N,N'*-dicyclohexylcarbodiimide (DCC) and aniline in *N,N*-dimethylformamide gave the same ketoamide **4** as had been previously obtained from enamine **2** and phenyl isocyanate. Direct proof for the position of substitution was not obtained in the other acylation products to be discussed.

Acyl derivatives were prepared by the reaction of enamine **2** with acid chlorides in the presence of triethylamine.= Reaction of **2** with acetyl chloride, propionyl chloride, benzoyl chloride, *p*-bromobenzoyl chloride, *p*-toluoyl chloride, and 3,4,5-trimethoxybenzoyl chloride, respectively, gave the corresponding β-diketones **6**–**11**.

Reaction of enamine **2** with 2,4-dichlorobenzoyl chloride afforded the diacylated product **12**. Some monosubstituted product was formed, as evidenced from the infrared spectrum of the crude material and the fact that certain fractions gave a positive ferric chloride test.



2 6, R = $-CH_3$; 7, R = $-C_2H_5$; 8, R = $-C_6H_5$; 9, R = $-C_6H_4$-*p*-Br; 10, R = $-C_6H_4$-*p*-CH_3; 11, R = 3,4,5-trimethoxyphenyl; 12

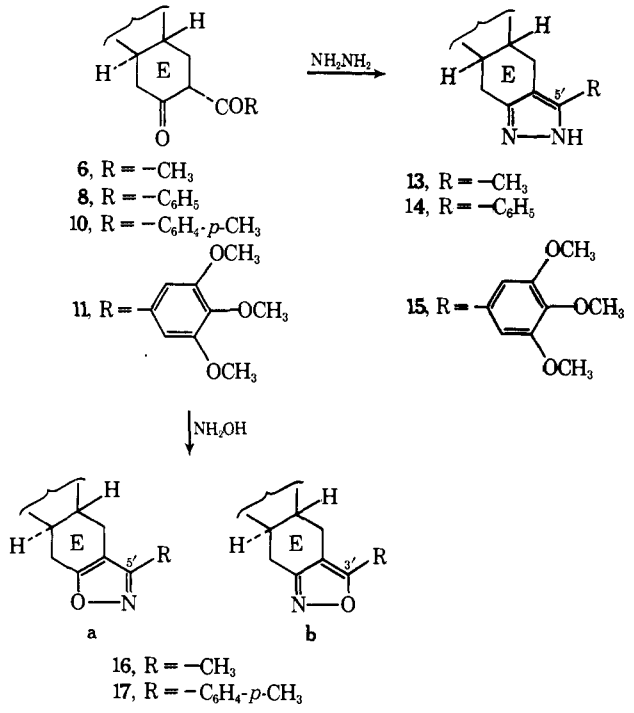
The reactions of these β-diketones with hydroxylamine, hydrazine, and guanidine were investigated. Reaction of β-diketones **6**, **8**, and **11** with hydrazine gave the corresponding 5′-substituted yohimbano[17,18-*c*]pyrazoles **13**–**15**. Heating β-diketones **6** and **10** with hydroxylamine gave isoxazoles **16** and **17**. Whether a mixture of **a** and **b** isomers was obtained (as anticipated) was not conclusively established. The pmr spectrum provided evidence for the presence of both **16a** and **16b** in the product from β-diketone **6** and hydroxylamine.

†For paper 8, see ref 1.

‡For acylation of enamines with isocyanates to give β-ketocarboxamides and dicarboxamides, see ref 3a. Clemmens and Emmons[3b] first reported this reaction but incorrectly identified the products.

§The chemistry of enamines has been reviewed by J. Szmuszkovicz.[4]

=For a discussion of alkylation and acylation of carbonyl compounds *via* enamines, see ref 5.



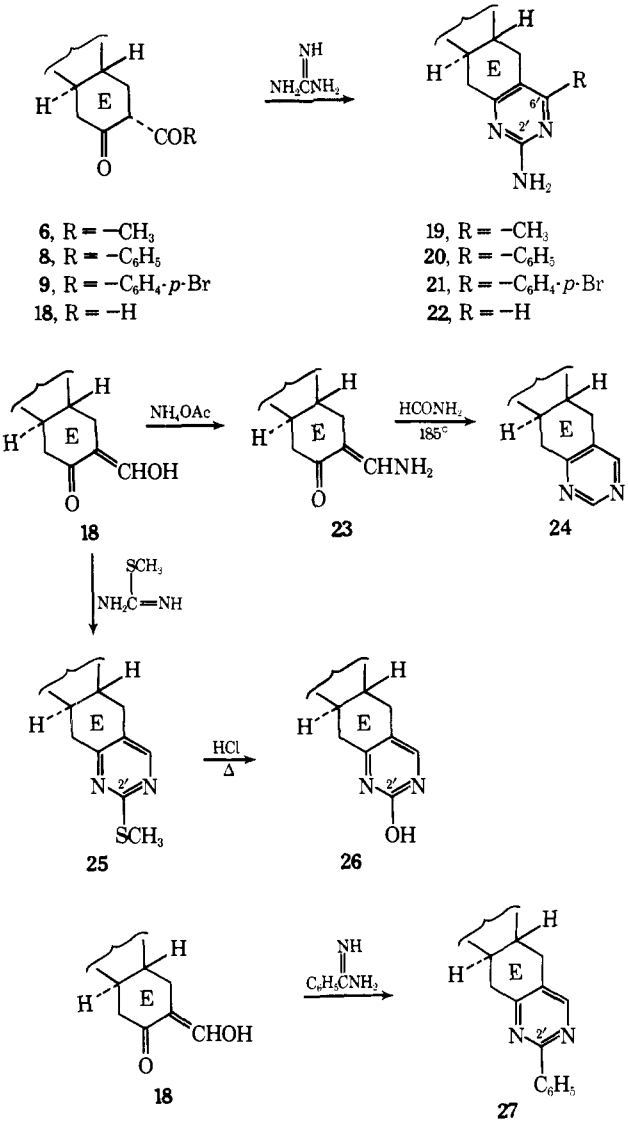
The synthesis of yohimbano[17,18-*d*]pyrimidines followed previously developed methods[6,7] for the preparation of simpler pyrimidines. Reaction of 18-hydroxymethyleneyohimban-17-one[2a] and 18-acylyohimban-17-ones with guanidine carbonate in refluxing ethanol gave the 2′-aminoyohimbano[17,18-*d*]pyrimidine derivatives **19**–**22** in moderate to low yields.

The unsubstituted pyrimidine **24** was prepared in 47% yield by heating the 18-aminomethylene ketone **23** with formamide at 185°. Reaction of 18-hydroxymethylene ketone **18** with 2-methyl-2-thiopseudourea gave the 2′-methylthiopyrimidine **25** which, on hydrolysis with concentrated hydrochloric acid, gave the 2′-hydroxypyrimidine derivative **26**. Reaction of **18** with benzamidine gave the 2′-phenylpyrimidine **27** in poor yield. Compounds are described in Table I and the Experimental Section.

Pharmacological Activity. In order to find potentially useful depressants of the CNS, the compounds described in this paper were screened to determine their effect on rod-walking ability and locomotor activity of mice.** The most interesting CNS depressants are listed in Table II. In contrast to yohimbano[17,18-*c*]pyrazole[2c] the 5′-methyl-substituted pyrazole **13** required high doses to impair rod-walking ability and locomotor activity of mice. These derivatives in Table II were the only ones in this report which exhibited motor depression (MDD_{50}) at doses of 100 mg/kg or less and all were relatively inactive in impairing rod-walking ability. Compounds **13**, **15**, **16**, **22**, and **25** were active hypotensives in conscious normotensive rats; however, all these derivatives (except **25**) produced adrenergic blockade.††

Experimental Section

Unless otherwise noted all melting points were taken in sealed capillaries which were inserted in a Mel-Temp apparatus 10–40° below the melting point and are uncorrected. Samples for analysis were dried *in vacuo* over P_2O_5 at 100° for 18–24 hr. Ultraviolet absorption spectra were measured on a Cary recording spectrophotometer. Infrared spectra were determined on a Perkin-Elmer spectrophotometer (Model 21). Pmr spectra were determined with



a Varian Model A-60 spectrometer in DMSO-d_6 or $CDCl_3$ with TMS as internal standard. Where analyses are indicated only by symbols of the elements or functions, analytical results obtained for those elements or functions were within ±0.4% of the theoretical values. Absorption bands (or peaks) of spectra (uv and ir) of compounds were as expected. Solvents were removed *in vacuo*.

17-Pyrrolidinylyohimb-17-ene (2). A mixture of 2.94 g (0.010 mol) of yohimban-17-one (**1**), 5.0 g of dry redistilled pyrrolidine, and 50 ml of sodium-dried C_6H_6 was refluxed for 18 hr in a Soxhlet extractor, the thimble of which contained Al_2O_3 to remove the H_2O azeotropically distilled. The resulting solution was concentrated, the residue was dissolved in 25 ml of $CHCl_3$ (dried over Al_2O_3), and the solvent was again removed. The residual pale reddish glass was heated at 90–100° under high vacuum for 2 hr to remove the last traces of pyrrolidine. Examination of the ir spectrum ($CHCl_3$) of the product showed only weak carbonyl absorption, equivalent to approximately 10% contamination with yohimban-17-one.

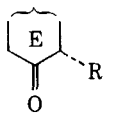
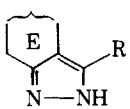
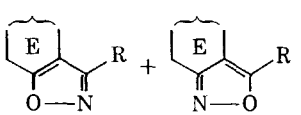
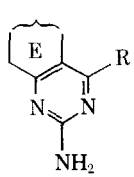
Procedure A. 17-Oxoyohimban-18α-carboxanilide (4). 1. To a cooled solution of 0.010 mol of **2** in 20 ml of C_6H_6 and 5 ml of $CHCl_3$ was added 0.95 ml of phenyl isocyanate. The mixture, under nitrogen, was allowed to stand at room temperature for 19.5 hr and the solvent was then removed.

The residue was stirred for 20 min with a mixture of 50 ml of $CHCl_3$, 25 ml of H_2O, and 4.0 ml of glacial AcOH and then brought to pH 7.5 with concentrated NH_4OH. The $CHCl_3$ layer was separated and the H_2O layer was extracted with $CHCl_3$. The extract was dried over Na_2SO_4 and the solvent was removed. The residue (5.0 g) was triturated with 50 ml of EtOAc and filtered. The filtrate, on standing, deposited 1.28 g (31%) of crystals of **4**, mp 208–210° dec. Recrystallization from aqueous EtOH with the aid of activated carbon and recrystallization from EtOH-$CHCl_3$ gave pale orange crystals.

**Pharmacological data were supplied by Dr. A. C. Osterberg and coworkers; for screening procedures, see ref 8.

††Hypotensive data were supplied by Dr. J. R. Cummings and coworkers.

Table I. 18-Acylyohimban-17-ones and Heterocyclic Derivatives

	R =	Procedure	Solvent	Yield, %	Mp, °C (dec)	Recrystn solvent	$\alpha^{25}D$, deg (*c*, solvent)	Formula[b]
								
4	$CONHC_6H_5$	A 1	C_6H_6–$CHCl_3$	31	218–219	EtOH–$CHCl_3$	−160 (0.90, DMF)	$C_{26}H_{27}N_3O_2 \cdot 0.5C_2H_5OH$
5	$CONHC_6H_4$-*p*-CH_3	A 1	CH_2Cl_2	45	236–238	EtOH–$CHCl_3$	−112 (1.2, AcOH)	$C_{27}H_{29}N_3O_2$
6	$COCH_3$	B	$CHCl_3$	22	275–280	EtOAc	−183 (1.1, pyridine)	$C_{21}H_{24}N_2O_2$
7	COC_2H_5	B	CH_2Cl_2	8	154–159	C_6H_6-C_6H_{12}		$C_{22}H_{26}N_2O_7$
7 HCl					268–272			$C_{22}H_{26}N_2O_2 \cdot HCl \cdot {}^1/_3H_2O$
8	COC_6H_5	B	$CHCl_3$	8	231–235	Me_2CO–H_2O	−206 (1.1, pyridine)	$C_{26}H_{26}N_2O_2 \cdot 0.25H_2O$
9	COC_6H_4-*p*-Br	B	CH_2Cl_2	35	241–244	Me_2CO	−103 (1.0, AcOH)	$C_{26}H_{25}N_2O_2Br$
10	COC_6H_4-*p*-CH_3	B	CH_2Cl_2	59	190–195	Me_2CO–H_2O	−104 (1.0, $CHCl_3$)	$C_{27}H_{28}N_2O_2 \cdot 0.25H_2O$
11	COC_6H_2-3,4,5-$(OCH_3)_3$	B	$CHCl_3$	18	226–229	EtOH–H_2O	−162 (1.4, pyridine)	$C_{29}H_{32}N_2O_5 \cdot 0.25H_2O$
								
13	CH_3	C	EtOH	48	310–313	MeOH–H_2O	−209 (1.0, pyridine)	$C_{21}H_{24}N_4$
14	C_6H_5	C[a]	EtOH	32	280–284	EtOH–H_2O	−260 (1.2, pyridine)	$C_{26}H_{26}N_4 \cdot 0.25H_2O$
15	C_6H_2-3,4,5-$(OCH_3)_3$	C[a]	EtOH	52	>210, sinters 190–210	MeOH	−232 (1.0, pyridine)	$C_{29}H_{32}N_4O_3 \cdot 0.25\ H_2O$
					 a + b			
16a + 16b	CH_3	D	EtOH	70	265–268	EtOH–H_2O	−199 (1.1, pyridine)	$C_{21}H_{23}N_3O$
17a + 17b	C_6H_4-*p*-CH_3	D	EtOH	56	300–302	$CHCl_3$-MeOH	−238 (1.0, pyridine)	$C_{27}H_{27}N_3O$
								
19	CH_3	E	EtOH	37	320–325	MeOH	−206 (1.0, pyridine)	$C_{22}H_{25}N_5$
20	C_6H_5	E	EtOH	42	>200, sinters 185	MeOH	−326 (1.3, pyridine)	$C_{27}H_{27}N_5 \cdot 0.25H_2O$
21	C_6H_4-*p*-Br	E	EtOH	3	207–211	Me_2CO	−294 (1.1, pyridine)	$C_{27}H_{26}N_5Br$
22	H	E	EtOH	42	313–316	MeOH	−208 (0.88, pyridine)	$C_{21}H_{23}N_5$

[a]Purified by direct crystallization without chromatography. [b]Analyses for C, H, N, and halogen (where applicable) were within ±0.4% of calculated values.

2. 17-Oxoyohimban-18-carboxylic acid hydrochloride (3)[2a] (2.0 g, 0.005 mol) was added to a mixture of 10 ml of DMF, 3.0 ml (3.0 g, 0.032 mol) of aniline, and 3.06 g (0.010 mol) of *N,N'*-dicyclohexylcarbodiimide. The mixture was stirred at room temperature for 24 hr and then 2 ml of H_2O and 1 ml of glacial AcOH were added. After being stirred for 2 hr the mixture was poured into 20 ml of 50% aqueous AcOH and filtered. The filtrate was made basic with concentrated NH_4OH and extracted with CH_2Cl_2. The extract was washed with H_2O, dried over $MgSO_4$, and concentrated. The red residue was dissolved in EtOAc and the solution was diluted with heptane. A dark gum separated and was removed by filtration. The filtrate was evaporated and the residue was dissolved in C_6H_6 and filtered through a column of 30 g of Florisil. The column was eluted with C_6H_6, the first 500 ml of eluate from the column was concentrated, and the residue was crystallized from EtOAc. The mixture was filtered, the filtrate was concentrated, and the residue was dissolved in MeOH and made acidic with concentrated HCl. On concentration some gummy solid separated and was discarded. Further concentration gave a gummy solid which was triturated with Et_2O-Me_2CO to give an off-white solid. This was dissolved in MeOH and the solution was made basic with concentrated NH_4OH. Dilution with H_2O and filtration gave 0.125 g of product. This was crystallized from aqueous ethanol to give 0.100 g (4.6%) of product as pale pink crystals, mp 219–222° dec. Further washing of the Florisil column with 600 ml of C_6H_6 and slow evaporation of the eluate gave an additional 0.030 g (1.3%) (total, 6%) of product as off-white crystals: mp 224–226° dec; mmp (with a sample prepared by procedure A 1 above) 224–226° dec; $[\alpha]^{25}D$ −150° (*c* 1.2, DMF). The ir spectrum (KBr) was identical with that of a sample prepared by procedure A 1 above. The sample gave a positive ferric chloride test.

Procedure B. 18-Acetylyohimban-17-one (6). To a chilled solution of 2 (prepared from 14.7 g of 1) in 100 ml of $CHCl_3$ was added 8.0 ml of dry triethylamine and 3.93 g of AcCl. After 17 hr at room temperature the mixture was worked up as for compound 4. The residue was triturated with EtOH and filtered to give 14.1 g of crystals. By repeated recrystallizations from MeOH and from EtOAc, yohimban-17-one was separated from the product and there was obtained 3.74 g (22%) of 6 as tan crystals, mp 223–226° dec. Recrystallization of a sample from EtOAc gave tan crystals.

On a larger scale run, when the reaction mixture was poured into aqueous AcOH and the mixture was stirred for 3 hr, a precipitate of the hydrochloride of the product separated, facilitating the work-up. Direct filtration gave the hydrochloride of 6 in 41% yield.

18-(2,4-Dichloro-α-hydroxybenzylidine)yohimban-17-one 2,4-Dichlorobenzoate (12). To enamine 2 (0.025 mol) in 72 ml of chilled CH_2Cl_2 and 25 ml of triethylamine under nitrogen was added 4.71 g (0.0225 mol) of 2,4-dichlorobenzoyl chloride. The mixture, after standing at room temperature for 17 hr, was worked up as for compound 4. The residue was triturated with a mixture of 100 ml of EtOH and 25 ml of H_2O. Filtration gave 7.0 g of tan crystals. The solid was dissolved in Me_2CO and the solution was treated with activated charcoal. Filtration and concentration of the filtrate to 100 ml gave, on cooling and filtering, 0.87 g of yohimban-17-one. Further concentration and dilution with H_2O gave 0.42 g of white crystals, mp 170–175° dec. Recrystallization, by dissolving in EtOH-$CHCl_3$ and concentrating the solution, gave 0.31 g (4%) of 12 as colorless rods: mp 182–185° dec; $[\alpha]^{25}D$ −87° (*c* 1.2, $CHCl_3$). *Anal.* ($C_{33}H_{26}N_2O_3Cl_4$) H, N, Cl; C: calcd, 61.9; found, 61.2.

Procedure C. 5'-Methylyohimbano[17,18-*c*]pyrazole (13). A mixture of 6.73 g of 6 · HCl, 150 ml of EtOH, and 1.0 ml of hydrazine hydrate was stirred at room temperature under nitrogen for 45 min and then refluxed for 3.5 hr. After standing overnight the solvent was removed to give the hydrochloride as tan crystals, mp 343–347° dec. The crystals were partitioned between 200 ml of $CHCl_3$, 50 ml of EtOH, and 200 ml of dilute aqueous NaOH. The $CHCl_3$ layer was separated and the H_2O layer was extracted with three 100-ml portions of $CHCl_3$. The combined extracts were dried over $MgSO_4$ and the solvent was removed *in vacuo* to give 7.3 g of a tan glass. The glass was dissolved in CH_2Cl_2 and chromatographed over neutral Al_2O_3. The product was eluted with CH_2Cl_2-MeOH (9:1) and crystallized from aqueous MeOH to give 3.71 g (62%) of tan crystals, mp 304–308° dec. Recrystallization from aqueous MeOH gave 2.90 g (48%) of 13 as tan crystals.

Procedure D. 5'-Methylyohimbano[17,18-*c*]isoxazole (16a) and 3'-Methylyohimbano[18,17-*d*]isoxazole (16b). A mixture of 4.04 g of 6, 0.973 g of hydroxylamine hydrochloride, and 300 ml of EtOH was refluxed for 3 hr. After being allowed to stand overnight the mixture was filtered to give 3.8 g of the product hydrochloride as tan crystals, mp 323–327° dec. The crystals were dissolved in 400 ml of hot EtOH-H_2O (1:1) and the solution was made basic with 10 *N* NaOH. The mixture was chilled and filtered to give 2.83 g (70%) of a mixture of 16a and 16b as tan crystals.

Table II. CNS Testing Results[a]

Compd	MDD_{50},[b] mg/kg	RWD_{50},[c] mg/kg	ISD_{50},[d] mg/kg
6	4	165	450
8	47	>800	
13	100	>500	>2000
22	5	425	>1000
23	13	140	450
24	23	100	>2000

[a] Compounds were administered to mice ip. No lethality was found at ISD_{50}. [b] The dose estimated to reduce motor activity in mice to 50% of controls. [c] The dose estimated to cause 50% of the mice to be incapable of walking across a horizontal rod in a normal manner. [d] The dose estimated to cause 50% of the mice to fall off a screen inclined at 60°.

Procedure E. 2'-Amino-6'-methylyohimbano[17,18-*d*]pyrimidine (19). A mixture of 1.35 g of 6, 0.378 g of guanidine carbonate, and 80 ml of EtOH was refluxed under nitrogen for 24 hr. The solvent was removed and the residue was partitioned between 100 ml of H_2O and 100 ml of $CHCl_3$. The $CHCl_3$ layer was separated, dried over $MgSO_4$, and concentrated to give 1.10 g of tan solid. Crystallization from MeOH afforded 0.53 g (37%) of 19 as pale yellow crystals, mp 290–295° dec (with sintering and decomposition above 260°). Recrystallization from MeOH gave 0.41 g of off-white crystals.

18-Aminomethyleneyohimban-17-one (23). A mixture of 45.0 g of 1, 45.0 g of $NaOCH_3$, 63 ml of ethyl formate, and 1.3 l. of dioxane was stirred under argon at room temperature for 21 hr. The mixture was adjusted to pH 5.0 with AcOH and the solvent was removed. The residue was treated with 220 ml of MeOH and 450 ml of H_2O and the solvent was removed. The residue was treated with concentrated NH_4OH until the pH was adjusted to 7. The mixture was filtered and the precipitate was slurried with MeOH. Filtration gave 25 g of 23 as tan crystals, mp 310–318° dec, with sintering to a dark mass above 270°. *Anal.* ($C_{21}H_{23}N_3O \cdot 0.5H_2O$) C, H, OCH_3; N: calcd, 12.7; found, 12.0.

Attempts to purify the product further were unsuccessful. Recrystallization from MeOH gave yellow needles, mp 314–319° dec (sinters to a dark mass above 270°); found for OCH_3, 1.20. The OCH_3 value indicates that some 18-methoxymethyleneyohimban-17-one was formed on recrystallization from MeOH.

Yohimbano[17,18-*d*]pyrimidine (24). A mixture of 10.0 g of 23 and 70 ml of formamide was stirred and heated under nitrogen at 185° for 4 hr. The mixture was cooled and poured into 450 ml of cold H_2O. Filtration gave a tan solid which was washed with water and then triturated with 250 ml of hot MeOH. The filtrate was chilled and filtered to give 4.7 g (47%) of tan crystals. These crystals were combined with 1.1 g of product from a similar run and recrystallized from Me_2CO with the aid of activated charcoal to give 2.58 g of 24 as tan crystals, mp 273–276° dec. Recrystallization from MeOH gave 24 as light tan rods: mp 278–281° dec; $[\alpha]^{25}D$ −215° (*c* 1.0, pyridine). *Anal.* ($C_{21}H_{22}N_4$) C, H, N.

2'-Methylthioyohimbano[17,18-*d*]pyrimidine (25). A mixture of 10.20 g of 18, 4.32 g of 2-methyl-2-thiopseudourea sulfate, 200 ml of EtOH, and 1.74 g of KOH was stirred at room temperature under nitrogen for 4 hr and then refluxed for 5 hr. The solvent was removed and the residue was washed thoroughly with H_2O. The residue was heated with a mixture of 1500 ml of CH_2Cl_2 and 1500 ml of Me_2CO and filtered. The filtrate was concentrated to an orange-yellow solid which was triturated with 250 ml of hot Me_2CO and filtered to give 4.10 g (36%) of 25 as yellow crystals, mp 273–276° dec. Recrystallization by dissolving in MeOH and CH_2Cl_2, treating with activated charcoal, filtering, and concentrating the filtrate on a steam bath until crystals began to separate gave 2.35 g (21%) of 25 as orange crystals, mp 280–285° dec. A 0.300-g sample was recrystallized by dissolving in CH_2Cl_2-MeOH (1:1) and concentrating the solution. Filtration gave 0.200 g of 25 as pale yellow-orange crystals: mp 280–283° dec; $[\alpha]^{25}D$ −184° (*c* 1.0, pyridine). *Anal.* ($C_{22}H_{24}N_4S$) C, H, N, S.

Yohimbano[17,18-*d*]pyrimidin-2-ol (26). A mixture of 0.336 g

of 25 and 15 ml of concentrated HCl was stirred and refluxed for 3 hr. An additional 5 ml of concentrated HCl was added and the mixture was refluxed for an additional 4 hr. The resulting yellow precipitate was removed by filtration and washed thoroughly with H_2O. The precipitate (0.335 g) was dissolved in hot 50% aqueous EtOH and the solution was made slightly basic by the addition of concentrated NH_4OH. Concentration of the solution gave a gel which was removed by filtration and crystallized from $CHCl_3$-MeOH to yield 0.145 g (49%) of **26** as tan crystals. Recrystallization from $CHCl_3$-MeOH afforded 0.055 g of **26** as tan crystals; mp 280–285° dec (with previous sintering). *Anal.* ($C_{21}H_{22}N_4O \cdot \frac{2}{3}H_2O$) C, H, N.

2′-Phenylyohimbano[17,18-*d*]pyrimidine (27). A mixture of 10.2 g of 18, 6.26 g of benzamidine hydrochloride, 2.0 g of KOH, and 100 ml of EtOH was stirred at room temperature for 20 hr and refluxed for 3.5 hr. The solvent was removed and the residue was triturated with H_2O. Filtration gave 4.44 g of solid which was washed with H_2O, dried, dissolved in $CHCl_3$-EtOH (99.5:0.5), and chromatographed over Al_2O_3 to give 1.48 g of product. Trituration with MeOH gave 0.98 g (8%) of **27** as yellow crystals: mp 304–307° dec; $[\alpha]^{25}D$ −165° (*c* 1.0, pyridine). *Anal.* ($C_{27}H_{26}N_4 \cdot 0.25H_2O$) C, H, N.

Acknowledgment. We wish to thank Mr. L. M. Brancone and his staff for elemental analyses and Mr. W. Fulmor and his staff for spectral determinations.

References

(1) W. E. Meyer, J. A. Coppola, and L. Goldman, *J. Pharm. Sci.*, **62**, 1199 (1973).
(2) (a) J. D. Albright, L. A. Mitscher, and L. Goldman, *J. Org. Chem.*, **28**, 38 (1963); (b) J. D. Albright and L. Goldman, *ibid*, **31**, 273 (1966); (c) *J. Med. Chem.*, **14**, 571 (1971).
(3) (a) G. A. Berchtold, *J. Org. Chem.*, **26**, 3043 (1961); (b) D. H. Clemmens and W. D. Emmons, *ibid.*, **26**, 767 (1961).
(4) J. Szmuszkovicz in "Advances in Organic Chemistry," R. A. Raphael, E. C. Taylor, and H. Wynberg, Ed., Vol. 4, Interscience, New York, N. Y., 1963, p 1.
(5) G. Stork and H. Landesman, *J. Amer. Chem. Soc.*, **78**, 5128 (1956); G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, and R. Terrell, *ibid.*, **85**, 207 (1963).
(6) J. A. Zderic, O. Halpern, H. Carpio, A. Ruiz, D. C. Limon, L. Magana, H. Jimenez, A. Bowers, and H. J. Ringold, *Chem. Ind. (London)*, 1625 (1960); E. Caspi and D. M. Piatak, *Experientia*, **19**, 465 (1963); L. L. Smith, D. M. Teller, and T. Foell, *J. Med. Chem.*, **6**, 330 (1963); J. H. Ackerman, G. O. Potts, A. L. Beyler, and R. O. Clinton, *ibid.*, **7**, 238 (1964).
(7) D. J. Brown in "The Chemistry of Heterocyclic Compounds," A. Weissberger, Ed., Vol. 16, Wiley-Interscience, New York, N. Y., 1962.
(8) W. B. Wright, H. J. Brabander, R. A. Hardy, Jr., and A. C. Osterberg, *J. Med. Chem.*, **9**, 852 (1966).

Ergot Alkaloids. Ergolines and Related Compounds as Inhibitors of Prolactin Release

John M. Cassady,* George S. Li, Ernest B. Spitzner, Heinz G. Floss,

Department of Medicinal Chemistry and Pharmacognosy, School of Pharmacy and Pharmacal Sciences, Purdue University, West Lafayette, Indiana 47907

and James A. Clemens

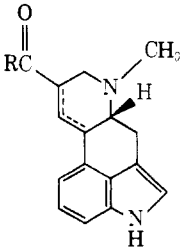
The Lilly Research Laboratories, Indianapolis, Indiana 46206. *Received August 14, 1973*

A number of naturally occurring ergot alkaloids, synthetic ergolines, and substituted indoles have been tested for their ability to inhibit the secretion of the hormone prolactin in rats. It has been established that the complete ergoline ring system is necessary for significant activity and that modifications of the D-ring portion of this system have a significant influence on prolactin-inhibiting activity. A number of compounds in the $\Delta^{8,9}$-ergoline series were tested and among these compounds elymoclavine showed very significant activity relative to ergocornine. A number of derivatives of elymoclavine also showed significant activity. In addition, several $\Delta^{9,10}$- and dihydroergolines were tested and although the $\Delta^{9,10}$ compounds were less active in general than the $\Delta^{8,9}$ series, several of the dihydroergolines showed good activity. Total synthesis of a series of ergolines with a cis C,D ring fusion (II series) was achieved from tricyclic ketone **6**. The testing results for these compounds indicate a decrease in prolactin-inhibiting activity.

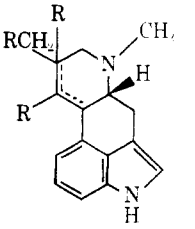
The ergot alkaloids consist of a series of 3,4-disubstituted derivatives of indole, the majority of which possess the tetracyclic ring structure designated as ergoline (I).

I

These alkaloids occur in various species of *Claviceps* including *Clavicèps purpurea* (Fries) Tulasne.[1,2] In addition, these compounds have been isolated from other closely related fungi[3] and certain species of the Convolvulaceae including *Ipomea*, *Rivea*, and *Argyreia*.[4] The naturally occurring ergot alkaloids can be conveniently divided into two groups according to their chemical structure,[1] the lysergic acid derivatives (II) and the clavines (III). The clavines are substituted 6,8-dimethylergolines and include a few members, namely the chanoclavines, with a 6,7-seco D ring.



II



III

The ergot alkaloids have a rich and varied history as therapeutic agents and several are currently used in the treatment of migraine and in the control of postpartum hemorrhage.[5] The lactation inhibitory effect of these compounds has long been recorded in the literature[6] but until recently had received little systematic attention. A series of studies, beginning with a report by Shelesnyak[7] in 1954 on the ability of ergotoxine to inhibit deciduoma formation, has now firmly established that ergolines inhibit lac-